

***REPORT ON THE BBSRC
SUCCEEDING IN
PLANT SYSTEMS BIOLOGY
WORKSHOP
24-25 JULY 2005
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EDINBURGH***



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SUMMARY

The principal objective of the *Succeeding in Plants Systems Biology* workshop was to stimulate thinking about the main requirements of systems biology approaches to plant science and to consider the advantages and problems in applying such approaches in research.

The workshop was open to all UK plant scientists (eligible to apply for funding within their own right) with an interest in using system-based approaches, and also to modellers and systems theorists with an interest in working on biological problems in the plant sciences. It was fully subsidised by the BBSRC and was organised in consultation with the co-ordinators of GARNet (UK Network for Arabidopsis functional genomics). Sixty three participants attended the workshop, including speakers and staff.

This report will be communicated to BBSRC's Integrative & Systems Biology Strategy Panel. It will also be made publicly available on the BBSRC website.

Disclaimer:

This report was produced by the BBSRC in consultation with others, as a result of a workshop attended by independent researchers. The report communicates a range of views, some of which are not necessarily those of the BBSRC.

1. BACKGROUND

- 1.1 BBSRC's Integrative & Systems Biology Panel met for the time in August 2004. One of the first tasks the Panel undertook was an appraisal of Expressions of Interest received to the first call of the BBSRC/EPSRC *Centres for Integrative Systems Biology* initiative. This funding call set out to establish the UK's first ever Systems Biology centres, with funding of up to £15M and £3M available from BBSRC and EPSRC respectively.
- 1.2 The Panel was concerned to find that relatively few plant biology-based applications were received to this call; furthermore, a serious concern was expressed that none of the plant-based applications were of sufficient quality to be short-listed. The Panel therefore recommended that BBSRC organises a special workshop to look into the issues surrounding the application of systems biology in plant science research.
- 1.3 *Succeeding in Plant Systems Biology* was the resulting workshop. The scientific content and structure of the programme was devised in collaboration with the co-ordinators of GARNet (Dr Ruth Bastow and Professor Andrew Millar). GARNet was created out of the BBSRC *Investigating Gene Function* (IGF) initiative, to ensure that functional genomic technologies were available to a wide user base. It has promoted and supported services such as transcriptome analysis, bioinformatics, metabolite profiling, proteome analysis and reverse and forward genetics for the *Arabidopsis* community. As an organisation representing a large part of the UK's plant science community (which is supported by the BBSRC for the greater part), GARNet was the obvious choice of partner for BBSRC to co-organise the workshop. Furthermore, the network is also scientifically well placed to consider future directions in the "post-genome" era.

2. AIM OF THE WORKSHOP

- 2.1 The main aim of this workshop was to identify what the current state of the art is in the use of systems-based approaches in plant science research, and where the challenges lie in taking up such approaches. Further details are given at Section 4.

3. ORGANIZATION AND SELECTION OF PARTICIPANTS

- 3.1 The workshop was advertised as being open to all researchers ordinarily eligible to apply for BBSRC funding (note that this did not necessarily exclude those in non-life science disciplines) – the workshop call, as appeared on the BBSRC website, is given at [Annex 1](#). Additionally, BBSRC drew upon the knowledge of the GARNet co-ordinators to issue invitations to specific individuals within the UK plant sciences research community. All those who registered were informed that, in allocating places at this workshop, the

BBSRC would take into consideration the need to have a balance of disciplines and wide institutional representation.

3.2 The workshop was undersubscribed by the research community, as up to 80 places were available; the number of invitations sent out by Dr Bastow (see paragraph 3.3) reflected the possibility that some individuals would not be able to attend due to prior engagements.

3.3 Workshop breakdown by numbers

Total number of participants:	60
– of which were staff:	4
– of which were speakers:	8
– of which were researchers registered via open call:	19 (of 23 registered)
– of which were researchers registered by invitation – life sciences:	18 (of 43 invited)
– of which were researchers registered by invitation – non life sciences:	11 (of 32 invited)

3.4 The rationale for restricting participation in this workshop to “eligible” researchers was that this event had been organised to look into the particular issues around the readiness of the plant sciences community to take post-genome science forward into systems biology research. Research leaders were considered best placed to address these issues; the workshop was therefore not suitable for junior scientists such as PhD students or postdoctoral assistants.

3.5 A conscious effort was made to enlist the participation of scientists outside the *Arabidopsis* research community, particularly researchers studying crop plants (cereals, legumes and Brassicas), mathematicians/modellers. This was considered essential for ensuring that the full remit of BBSRC science (and its interfaces with both physical and applied/environmental sciences) was covered. In terms of success in achieving this, a good proportion of attendees were mathematicians; it proved relatively difficult to secure the participation of crop scientists. A full list of all participants is provided at Annex 2.

4. WORKSHOP PROGRAMME

4.1 The scientific content of the programme was decided in consultation with Dr Ruth Bastow and Professor Andrew Millar. The programme was split into several themes, with time included for in-depth discussion in breakout sessions. The workshop programme is given at Annex 3. Themes were organised with an element of education in mind with respect to systems biology and modelling.

- 4.2 Plenary talks were grouped under themes in the workshop. Themes were chosen to stimulate thinking and discussion about the viability of systems-based approaches in the plant sciences. These were:
- What is systems biology and why is it of use?
 - How modelling can be of use to plant biology
 - Challenges and barriers to plant science systems biology
 - Large data sets
 - Quantitative data modelling
- 4.3 Delegates were assigned to four subgroups ([Annex 4](#)) to consider *Challenges and barriers to plant science systems biology*. Groups were of mixed disciplines, and were given the same set of questions to consider (below). Each was assigned a Chair and a Co-Chair to report back to the main group and asked to produce a poster of responses to the questions below.
1. What advantages might systems biology offer to plant science?
 2. What areas of plant science might be particularly amenable to such approaches?
 3. What are the current technical and other barriers in applying systems-biology approaches to plant science research?
 4. What scientific expertise can the UK in particular offer in this context?
 5. Are there any alternative approaches in plant science to *predictive biology*?
- 4.4 Additionally, delegates were provided with a summary of BBSRC's position ([Annex 5](#)) and an article on Systems Biology from *BIOForum Europe* journal, ([Annex 6](#)).
- 4.5 Posters produced in breakout sessions were displayed during informal networking time, and materials were provided for delegates to add comments in response, or in addition, to those on the posters. This was done to ensure that everyone was given the opportunity to articulate their views.
- 4.6 The final plenary session of the workshop was given over to general discussion and feedback.

5. OUTCOMES

- 5.1 In general, there were few comments about the questions that were being asked of the groups (see paragraph 4.3), except that some bemusement was expressed at question 5: some delegates asked whether this was a “trick question” (see paragraph 7.1).
- 5.2 Summaries of outcomes to each question are provided here. These are based on a comprehensive table of responses, provided at [Annex 7](#).

5.2.1 Q1 What advantages might systems biology offer to plant sciences?

Common themes

Formal representation as a 'system' allows:

- ❖ Better comparison between organisms
- ❖ Integration of disciplines/holistic
- ❖ Scalability from pathways and subsystems to landscapes
- ❖ Common structures for data collection, analysis and design
- ❖ Mathematical abstraction with predictive power
 - maximising information capture from large datasets
 - definition of gene function without making multiple knock outs
- ❖ Re-evaluate your assumptions, formalise your questions - new way of thinking about science

Additional Comments

- ❖ Opportunity to evolve models *in silico*
- ❖ Databases with common access language
- ❖ Development of new tools e.g. single cell sampling (*in planta*)
- ❖ Identifies gaps in present knowledge

5.2.2 Q2 What areas of the plant sciences might be particularly amenable to such approaches?

Possible Areas/topics

- ❖ All areas are amenable to a systems approach from single cells to ecology, and even the landscape
- ❖ Topics to focus
 - Environmental responses
 - The leaf as a system- Including young to old, guard cells, growth, senescence, stress, environmental change, sink to source, diverse cell types.
 - Plant Pathogen Interactions

Additional Comments

Plants offer a number of advantages

- ❖ Sessile, therefore simpler to model
- ❖ Strength of genetics
 - Recombinant inbred lines
 - Association mapping
- ❖ Spatial Organisation
 - Internal Algebra of plant growth (e.g. root) reduces no. of dimensions to study
- ❖ The system is readily manipulable: transgenic plants with altered 'dose' of a component can be constructed to test quantitative hypotheses.
- ❖ Easier ethical issues attached to plant experimentation versus animal

5.2.3 Q3 What are the current technical and other barriers in applying systems-biology approaches to plant research?

Common Themes

- ❖ Lack of multidisciplinary training (MSc, PhD)
- ❖ Poor communication with other disciplines, need to develop common languages.
- ❖ Lack of “best practice” for data handling
 - Need Standardisations/Organisation of data and protocols
- ❖ No existing comprehensive databases
 - Capture data at source, access via a federate system such as PLANET
- ❖ Spatial heterogeneity (many cell types contribute to each data point)
 - Lack of single cell sampling techniques

Additional Comments

- ❖ Perception of plant science: GM debate etc.
- ❖ Lack of examples of good predictive models that have been demonstrated to work.
- ❖ Modellers/experimentalists must work as one (and this takes time).
- ❖ Project Timescales are too short to develop interdisciplinary research.
- ❖ No good homogenous Arabidopsis cell culture.

5.2.4 Q4 What scientific expertise can the UK in particular offer in this context?

Common Themes

- ❖ Broad excellence in plant science, computational biology and informatics (not always well connected)
- ❖ Numerous resources
 - Germplasm collections in a range of species
 - Large data sets e.g. Transcriptomic data sets (NASC)
 - Genomic databases
- ❖ Strong, well-integrated (in parts) plant community
- ❖ Wide range of species studied

Additional Comments

- ❖ Centralised resources
 - NASC
 - Metabolomics at Rothamsted and Aberystwyth
- ❖ Large crop databases; breeding *in silico*, running scenarios under different environment- ability to predict phenotypes in changing environments, translate cross species, natural diversity
- ❖ Whole organisms/population biology
- ❖ International strength in plant biochemistry and modelling (MCA)
- ❖ Well developed Math-Biology community

5.2.5 General Conclusions from Wrap-up Session

Common Themes

- ❖ Standardization required
 - Data
 - Growth conditions
 - Publicly available databases
- ❖ Plant science has experience of scales larger than the individual
- ❖ Response to Environment could be a good umbrella topic for a dispersed UK systems biology project in plant sciences.

The ways forward.

- ❖ Need to make the best of the existing, dispersed systems expertise in plant research community by ensuring communication is maintained across institutions: network of interdisciplinary projects.
- ❖ Give plant scientists direct access to a theoretician via a short-term study group? This would be a potential mechanism for researchers to interact with theoreticians and discuss their research question in maths arena. Requires preliminary work to formulate questions appropriately.
- ❖ Networking among existing modellers in plant science, more experienced modellers could assist those just starting out: a theoretical plant science network, with regular workshops?

Additional comments

- ❖ Systems biology, especially in plants, requires a longer timeframe than the 3-year grant cycle to establish interdisciplinary work.
- ❖ Remember the cross-council discipline-hopping awards
- ❖ Consider internships for undergraduate Maths students in plant science

Problems from a Maths perspective

- ❖ Lack of theoreticians at present, need to increase training across the maths biology interface: interdisciplinary PhDs.
- ❖ Plant Science is competing for biological mathematicians scarce time with more popular topics e.g., cancer, so need a clear and visible focus to make the area more attractive e.g. first *in silico* plant, 2017 project. However the openness of plant scientists to collaboration is a strong point in their favour.
- ❖ Publicly available data of good quality is a key attraction for mathematical biologists.
- ❖ Data often too noisy to attract good theoreticians, so need to plan experiments after speaking to maths departments; alternatively, noisy data is an interesting mathematical challenge.

Problems from a plant perspective

- ❖ A lot of data already generated from the crops is available but not presently used.
- ❖ Cannot easily explain ideas to mathematicians need an intermediary or interpreter.
- ❖ Systems biology is presently defined around a single cell perspective which is hard to apply to research in multicellular organisms.

6. MAIN FINDINGS & CONSENSUS

- 6.1 Several common issues emerged from the breakout sessions and the plenary discussion which followed.
- 6.1.1 *Advantages of using Systems Biology approaches in plant sciences* would include the ability to model across scales, predictive approaches aiding experimental design/hypothesis testing and the development of common experimental procedures, data formats and methods to access data, which would also be a powerful aid to research.
- 6.1.2 *Areas of plant science considered amendable to systems-based approaches* were not restricted, and although specific areas were cited, they were generally to be found across the range of plant biology.
- 6.1.3 *Current barriers to applying Systems Biology to research* were the lack of comparable or common data standards, a lack of modellers engaged in plant science research and a communication/outreach barrier between plant science and other disciplines. The relatively long timescales of plant science and of systems biology will need to be matched by suitably stable funding mechanisms.
- 6.1.4 *Scientific expertise which the UK plant science community could offer* included world-class expertise in genomic and post-genomic science, a well networked community with a strong sense of identity both in model and crop species, and a good track record in establishing and maintaining shared resources (e.g. NASC, MetRO).
- 6.1.5 It was agreed that apart from systems biology, there were no *alternative approaches to achieving predictive biology*.

7. ANALYSIS – BBSRC PERSPECTIVE

- 7.1 This question regarding alternative approaches to predictive biology was asked in order to provoke thinking about the importance of systems biology, particularly in the future. It was inspired by BBSRC's Ten Year Vision (see <http://www.bbsrc.ac.uk/about/pub/policy/vision.html>), which was published in 2003 after extensive consultation with the research community. In summary, the Vision states that genome sequencing and post-genomic technologies have provided researchers with massive amounts of data; as a consequence biology is becoming more quantitative. This vision sees the opportunity to use the large amounts of data that are now accumulating to better understand the function and behaviour of plants, animals and microbes at all levels, from molecules to populations – thus signalling a move towards more integrative approaches in the study of living organisms. Large experimental data sets will increasingly allow *in silico* simulation of biological systems, e.g., a model of a basic living cell. Thus the answer to the question of alternatives to systems biology as being “No” in this workshop confirmed the view that systems

biology (in the loose characterisation presented to the workshop, see paragraph 7.2.1) is the best way to practically deal with biology becoming increasingly predictive.

- 7.2.1 In the plenary discussion, comments made in breakout sessions (see paragraph 6.1) were reiterated and expanded upon. The current BBSRC (and EPSRC) position on systems biology as a scientific approach avoids being overly prescriptive. BBSRC and EPSRC acknowledge that there are many different definitions of systems biology, and many possible approaches to the development of systems biology research, appropriate to different research challenges; BBSRC's Integrative & Systems Biology Panel (responsible for developing the council's policies in this area) therefore drew up an *indicative* list of key characteristics ([Annex 5](#)). These criteria were used in appraising applications to the BBSRC/EPSRC *Centres for Integrative Systems Biology* initiative.
- 7.2.2 Delegates at this workshop asserted that systems biology-based research would require multidisciplinary/interdisciplinary research teams, and the issue of bridging the disciplines gap was raised in the plenary discussion. Mathematics-based approaches to experimental design were not considered beyond the pale for plant biology, but the consensus was that the discipline needed to be better “marketed”, as it were, to attract the right people. Most delegates agreed that time and effort would need to be invested in actively attracting modellers and theoreticians to plant science research – they were needed from the outset of project planning in order to formulate the right questions to investigate through experimentation (one comment made was that biologists have difficulty asking the right questions). The principle of involving relevant non-life scientists in developing systems biology approaches is firmly aligned with the view of the ISB Panel. There may well be a need to get the view from mathematics community regarding their availability to work with plant scientists. It was also suggested that mathematicians needed “big goals” to work towards; plant scientists therefore needed to articulate the big questions and communicate these to mathematicians.
- 7.2.3 Additionally, a feeling was expressed in this workshop that while plant biology research was critically important on a global scale (i.e. outside the intellectual endeavour itself for scientists), this seemingly obvious fact was being “out-competed” in society by other science areas – cancer research being a notable example. Delegates thought that the onus was on the plant sciences research community to compete better in this kind of beauty contest.
- 7.2.4 This issue of attracting the right researchers is, naturally, closely tied in with training, which was also mentioned in discussions – although questions of training are by no means unique here, there was thought to be a real need to attract promising students into PhD and Masters Courses, in both plant science and mathematics. It should be noted that BBSRC and EPSRC consider specific training in systems biology itself to be of prime importance in achieving critical mass in this area in the UK.

- 7.2.5 In discussion of disciplinary gaps, the issue of models vs. crop species was also touched upon: a suggestion was made that crop science needed to be “brought in from the cold”, and crop species modellers in particular may have valuable expertise to offer in the context of systems biology. BBSRC’s ISB Panel recently reiterated that the council’s “big tent” approach to systems biology was the right one to take, in that all disciplines with BBSRC remit should in theory be considered as potentially suitable for Systems Biology research – how viable this is in reality is a question for the research community to address. The issue of models vs. crops needs to be addressed by the research community; it would appear that *Arabidopsis* presents the most viable species in which to potentially exploit opportunities in system biology research – as a first step. Reasons for this include availability of the genome sequence, prior investment in post-genomic science to build upon, and an established research community with international profile and identity, which has a track record in co-operation for resource sharing. The plant science community should ensure however, that crop science funded by the BBSRC is given due consideration regarding the feasibility of systems-based approaches, and should communicate its views on this to the BBSRC.
- 7.2.6 Data generation and handling were cited several times in the workshop as areas of particular concern. BBSRC shares these concerns, particularly those of data sharing and data standards; it is therefore in fact a positive step that these issues were raised by the community itself at this workshop. BBSRC’s Tools & Resources Panel is currently leading on producing a Data Sharing Policy. Having such a policy will be essential for managing outcomes from systems biology research funded by BBSRC/EPSRC. It is therefore important for the plant science community to take the standardisation and sharing issue into account from the outset when considering the use of systems-based approaches.
- 7.2.7 The issue of physical centres vs. a distributed network was also considered. The ISB Panel is currently in early stage discussions regarding mechanism(s) to disburse BBSRC’s Spending Review 2004 settlement for systems biology, with further funding to be available beyond the current initiative to establish large centres. The weight of opinion at this meeting in regard to future funding seemed inclined towards the distributed network model; the question is, therefore, whether GARNet could form the basis of a “next generation” network to deliver systems biology research in plants, through a dispersed funding mechanism. BBSRC is neutral on this question at present, and awaits a response from the community: the issue is currently out to consultation via the GARNet steering committee. The report from GARNet will contribute to BBSRC’s strategic planning.

8. PRACTICAL SUGGESTIONS

- 8.1 Several suggestions were made about how the plant science community might begin to practically realize a move towards systems biology-based research, at smaller scales than the network funding of systems biology projects. These included:

- Cases to be made for PhD and MSc training in both plant biology and mathematics where opportunities arise.
- Consider a low threshold mechanism for entry into systems modelling, as GARNet did with microarrays, for example (described by one delegate as a “toe in the water” activity), such as mathematical study groups to be hosted by universities – such groups are established in Mathematics & Medicine at the University of Oxford, for example.
- Further networking between plant scientists and mathematicians/computer scientists, including researchers in crop modelling.
- Consider a project by which to unite the network, for example “Systems Biology of a Leaf”.
- Research a set of best practice guidelines for systems-based approaches in plant biology.
- Consider the possibility of the using the Research Councils’ Discipline Hopping Scheme, and encourage BBSRC to cite plant science within the scheme.
- Consider the possibility of promoting internships for final year Mathematics Bachelors in plant biology labs.
- Approach the Newton Institute about running an “immersion course” in plant science.

9. CONCLUDING REMARKS

- 9.1 GARNet, which was established through BBSRC funding, provides a ready-made network which the council can draw upon (though not exclusively so) for consultation regarding post-genomic science strategy development in plant biology. This workshop was organised in close consultation with the GARNet coordinators to draw upon this expertise, and also to provide the community with an opportunity to be introduced to systems biology as circumscribed by BBSRC and EPSRC.
- 9.2 The workshop was somewhat undersubscribed, but the most plausible explanations for this are one or both of two factors: participation was restricted to those ordinarily eligible to apply for BBSRC funding (i.e. those who would apply to BBSRC as named Investigators) and/or dates set were incompatible with diaries.
- 9.3 It proved relatively difficult for the workshop organisers to enlist the participation of research communities outside the *Arabidopsis* sphere. However, in terms of success in achieving diversity of disciplines, a good number of mathematicians attended the workshop.
- 9.4 The workshop was felt to be successful as a first formal event for the BBSRC-funded plant biology community to learn more about what systems biology involves, and consider what activities this may necessitate scientifically and strategically. This is evidenced by the lively discussions which took place, and the practical suggestions that were made as a result. On this positive note, BBSRC would be willing to consider organizing a second event of this sort

(possibly in late 2006/early 2007) if effort is made by the research community in advancing the agenda in the interim.

10. ACKNOWLEDGMENTS

BBSRC expresses its gratitude to:

Dr Ruth Bastow and **Professor Andrew Millar** for their input in setting the scientific programme for the workshop, and securing the participation of invited speakers;

Speakers as listed at [Annex 3](#) for their particular contributions to the programme;

Professor Richard Baldock, Professor Andrew Bangham, Professor Igor Goryanin, Dr Murray Grant, Professor Jonathan Jones, Professor Keith Lindsey, Professor David Rand and **Professor Simon Turner** for acting as Chairs/Co-Chairs of the breakout sessions;

Professor Olaf Wolkenhauer for kind permission to use his co-authored article on Systems Biology, as published in *BIOForum Europe*.

BBSRC Website Notice

Succeeding in Plant Systems Biology

Monday 25 - Tuesday 26 July 2005, Marriott Dalmahoy Hotel & Country Club, Edinburgh

BBSRC is pleased announce this special workshop, which aims to consider the challenges involved in successfully applying integrative and systems biology approaches to plant science research.

The principal objective of the workshop is to stimulate awareness of the main requirements of systems biology approaches amongst plant scientists and to consider the special problems and needs in applying such approaches to plant science research.

The programme for the workshop is to be confirmed, but will include world class speakers from the plant sciences and other disciplines to facilitate the intellectual links that need to be made in applying systems-based approaches to plant research. A significant amount of time will be devoted to networking and in-depth discussions on:

- What the scientific and other challenges and barriers are to applying system-biology approaches in plant science research
- How these might be effectively addressed

This workshop is open to all UK plant scientists (eligible to apply for funding within their own right) who have an interest in using system-based approaches, and also to modellers and systems theorists who have an interest in working on biological problems in the plant sciences.

In allocating places at this workshop, the BBSRC will take into consideration the need to have a balance of plant scientists and systems theorists and modellers etc., and a wide institutional representation. As usual with BBSRC workshops, accommodation and meals are fully subsidised, but attendees must meet their own travel expenses and associated subsistence costs.

Further details, including the application process, will become available shortly, but the workshop is likely to commence at 11am on 25 July, and conclude by 3pm on the 26 July.

The workshop is being organised in collaboration with the GARNet network (Dr Ruth Bastow):

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“Succeeding in plant systems biology” 25-26 July Edinburgh

Day 1

09:00 – 11:00 Registration
11:00-11:30 Welcome Andrew Millar/Alf Game BBSRC

What is Systems Biology and why is it of use?

11:30 – 13:00
Charlie Hodgman, University of Nottingham, UK
Steve Oliver, University of Manchester, UK

13:00 – 14:00 Lunch

How modelling can be of use to plant biology

14:00 – 15:30
Cris Kuhlemeier, University of Bern, Switzerland
Kazuki Saito, Chiba University, Japan

15:30– 16:00 Tea Break

Challenges and barriers to Plant science systems Biology

16:00 – 18:00 Breakout and Discussions

18:00 – 19:30 Drinks Reception and Networking

19:30 Dinner and After Dinner Speaker
 Professor Andrew Millar, University of Edinburgh

Day 2

Large Data Sets

09:00 - 10:30
Chris Rawlings, Rothamsted Research, UK
Matej Oresic, VTT, Finland

10:30 – 11:00 Coffee Break

Quantitative Data Modelling

11:00 – 12:30
Jaroslav Stark, Imperial College London, UK
Martin Kuiper, University of Gent, Belgium

12:30 – 13:30 Lunch

Wrap-up

13:30 – 15:00

15:00 -15:30 Tea and Departures

Group1				
Secretary Alf Game				
Chair	Prof	Simon	Turner	Manchester
Chair	Prof	David	Rand	Warwick
Second	Prof	Mike	Bevan	JIC
	Dr	Peter	Craufurd	Reading
	Dr	Sean	May	Nottingham
	Prof	Howard	Thomas	IGER
	Prof	Steve	Oliver	Manchester
	Dr	Graham	Seymour	Warwick
	Prof	Ross	King	Aberystwyth
	Dr	Heiko	Rischer	VTT
	Dr	James	Cussens	York
	Dr	Christopher	Howe	Cambridge
	Dr	David	Westhead	Leeds
	Dr	Stephen	Baigent	UCL

Group2				
Secretary Ruth Bastow				
Chair	Prof	Jonathan	Jones	JIC
Chair	Prof	Andrew	Bangam	UEA
Second	Prof	Alistair	Hetherington	Lancaster
	Dr	Guy	Barker	Wellesbourne
	Prof	Chris	Cannings	Sheffield
	Prof	Jim	Haseloff	Cambridge
	Dr	Kazuki	Saito	Chiba University
	Prof	Phil	Mullineaux	Essex
	Dr	Chris	West	Leeds
	Dr	Janet	Taylor	IGER
	Dr	Chris	Rawlings	Rothamsted
		Marcus	Tindall	Oxford
	Mr	Michael	Watson	IAH Compton
	Dr	Reidun	Twarock	York
	Dr	Douglas	Armstrong	Edinburgh

Group 3				
Secretary Sophia Abbasi				
Chair	Prof	Keith	Lindsey	Durham
Chair	Prof	Richard	Baldock	MRC Edinburgh
Second	Dr	Anna	Amtmann	Glasgow
	Prof	Jim	Beynon	Wellesbourne
	Prof	Andrew	Millar	Edinburgh
	Dr	Alex	Webb	Cambridge
	Prof	Charlie	Hodgman	Nottingham
	Dr	Heather	MacDonald	UWE
	Prof	John	Draper	Aberystwyth
	Dr	Gerard	Bishop	Imperial Wye
	Dr	Helen	Ougham	IGER
	Prof	Jaroslav	Stark	Imperial
	Dr	Bruce	Marshall	SCRI
	Mr	Paul	Verrier	R-Res

Group 4				
Secretary Vicky Buchanan-Wollaston				
Chair	Dr	Murray	Grant	Wye
Chair	Prof	Igor	Goryanin	Edinburgh
Second	Prof	Ian	Graham	York
	Dr	Graham	King	Rothamsted
	Prof	Ottoline	Leyser	York
	Prof	Cris	Kuhlemeier	University of Bern
	Dr	Vicky	Buchanan-Wol	Warwick
	Dr	Peter	Doerner	Edinburgh
	Dr	John	Carr	Cambridge
	Prof	Vincent	Moulton	UEA
	Dr	Martin	Kuiper	University of Gent
	Dr	Michael	Abberton	IGER
	Prof	Mark	Page	Reading

DELEGATES' INFORMATION SHEET FOR BREAKOUT SESSIONS

The main aim of this BBSRC workshop is to identify what the current state of the art is in the use of systems-based approaches in plant science research, and where the challenges lie in taking up such approaches. The breakout and networking sessions scheduled for the afternoon of Monday 25 July will provide an opportunity for in-depth discussion of relevant issues.

What are the features of a systems biology approach?

There are many different definitions of systems biology, and many possible approaches to the development of systems biology research, appropriate to different research challenges, but the following list identifies key characteristics of such approaches:

- An integrative approach to the subject area. This means research involving all components in the system being studied, at all relevant levels of biological organisation. This is normally an approach linked to knowing the genome, or having an otherwise well-characterised biological model.
- Access and ability to generate large experimental datasets. These will often be generated from high-throughput (HTP) technologies, and will be associated with the necessary data capture, handling and storage skills and facilities.
- The capability of undertaking predictive biology; the ability to manipulate the experimental data, and to develop the theoretical base (modelling) to understand those data, to test ideas and to optimise the next hypotheses to be tested experimentally.
- A mix of inputs from the biological, physical, engineering, mathematical and computational sciences.

The result is an iterative interaction between experiments and modelling. Scalability is a major advantage of the systems approach: mathematical models make it possible to analyse and understand much larger data sets than the simple, logical models that are implicit in all scientific reasoning.

Issues for further discussion in this workshop

Breakout sessions will be structured around the questions below; you may therefore find it useful to consider these ahead of Monday afternoon.

- 1. What advantages might systems biology offer to plant science?**
- 2. What areas of plant science might be particularly amenable to such approaches?**
- 3. What are the current technical and other barriers in applying systems-biology approaches to plant science research?**
- 4. What scientific expertise can the UK in particular offer in this context?**
- 5. Are there any alternative approaches in plant science to *predictive biology*?**

Systems Biology:

From a Buzzword to a Life Sciences Approach

The last 18 months have brought important changes to the field of Systems Biology. While in the beginning it was largely associated with some outstanding individuals, working in isolation, it is now accepted as a new discipline open to researchers from a range of disciplines. Numerous Centres and professorial positions have been established at Universities worldwide. Together with the appearance of a new focussed IEE Journal Systems Biology (www.iee.org/sb) there is sufficient evidence for a longer lasting affair of and biology with systems theory.

For any emerging area of research there is a risk that at some point in future it is looked at as a buzzword with all its negative connotations. There are two main causes for this to happen: individuals (mis)use the new term as a means to attract research funding through relabeling old ideas and without actually embracing new approaches. Secondly an area can simply fail, for scientific reasons to realise the promises it made. What is therefore called for is a definition of systems biology that provides a realistic attitude towards the opportunities and hurdles of this field. In our view, systems biology is about methodologies, i.e., data-based mathematical modelling and simulation, that help an understanding of the dynamic interactions of cells and components within cells. For this vision to succeed, we require foremost experiments and technologies that generate quantitative, time-resolved data.

Definitions of Systems Biology

There are two prevailing interpretations of what Systems Biology is about: a) the integration of data, obtained from experiments at various levels and associated with the "omics family" of technologies, and b) the dynamic interactions of gene products, proteins and cells that bring about the structure and function of cells, respectively higher levels of organisation, such as for example tissue, organs etc. The first view is more an informatics perspective, developing tools for data integration and fusion, while the second approach is motivated by data-based mathematical modelling and simulation. The first camp would often motivate their

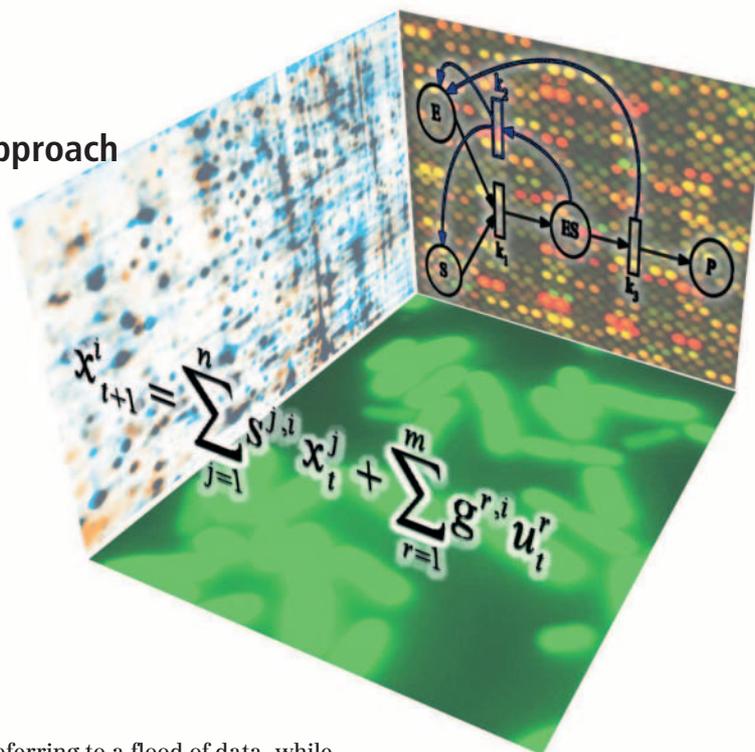
work by referring to a flood of data, while those interested in dynamic modelling of pathways are worried about the lack of quantitative, sufficiently rich data sets.

It is only natural that researchers, in their quest for research funds, develop an unexpected interest in new and emerging areas of research. While Systems Biology covers a broad spectrum of problems in the life sciences, to pass a test for a systems biology approach one must always be able to explain how the work relates to systems theory, specifically dynamic systems theory. The term "systems" in "Systems Biology" is, since the 1960s, associated with dynamic interactions, mathematical modelling, and simulation of biological pathways and networks. Fortunately this aspect of Systems Biology is not up for discussion.

Systems Biology signals a move away from just cataloguing and molecular characterisation of the components in cells, towards an understanding of the functionality and function of cellular networks. This requires more mathematical modelling than is comfortable for some scientists, and it has subsequently become common practice to replace the term "mathematical" with "computational" in an attempt to hide this fact.

The Systems Biology Approach

The complexity of molecular systems is fascinating and provides many interesting challenges for theoreticians with an interest in mathematical modelling and simulation. The overused term complexity is, in the context of systems biology, clearly defined



- the difficulties in dealing with many variables that are nonlinearly related in hierarchical, multilayered networks: observability,
- the difficulties in generating quantitative stimulus-response time series data: measurability,
- the difficulties in accounting for uncertainty, arising from a lack of observability and measureability.

The aim is that Systems Biology takes Genomics and Bioinformatics towards their natural conclusion – an understanding of the function and functioning of inter- and intra-cellular networks. For this programme to succeed, it is essential, that the area attracts new people for their different perspective. The emphasis is on methodologies rather than tools and technologies. Software tools are in this context only a means to an end. More important than computing power and software tools are measurement technologies and complex designs of experiments for generating data that are suitable for a systems approach. It is a well known fact from systems theory that the behaviour of a dynamic system can only be understood if it is systematically perturbed. This implies that we have to be in a position to define input signals, keep other variables constant, while observing output variables evolve over time. The need for repeated stimulus-response experiments highlights the need for a rethinking on behalf of the experimentalists.

The modelling process itself is more important than the model. The discussion between the experimentalist and the theoretician, to decide which variables to

measure and why, how to formally represent interactions in a mathematical form is the basis for successful interdisciplinary research in Systems Biology. In light of the complexity of molecular systems and the available experimental data, Systems Biology is the art of making the right assumptions in modelling. The modelling process and the model are to complement the biologist's reasoning – no more but no less either. Systems Biology is however not “holistic”. We cannot escape the reductionist approach that defines science. The complexity of systems in molecular and cell biology makes it necessary to focus on subsystems, study the whole through its parts, looked at in isolation. For a multi-level and multiple technologies approach the term “integrative” may be more appropriate. The current interest in “modules” and “motifs” of biochemical networks illustrates this. Systems Biology will hopefully bring about a new era in the life sciences but this is certainly not going to happen by means of “new age” approaches.

We should be under no illusion that it would be possible to build precise and accurate models of a cell or even organs. The concept of a “virtual cell” carries the risk of repeating the promises and failures in other areas, including for example Artificial Intelligence. The good news is that despite the complexity of these systems, successful examples of Systems Biology projects have already shown that it is possible to build predictive and useful models.

The cell is made up of molecules, like a car is made up from plastic and metal. But a soup of molecules is no more a cell than a heap of plastic and metal is a car. To understand the functioning and function of a cell we need to know the (static) relations and understand the (dynamic) interactions among the components that constitute it.

Example of a European Initiative

Within the European Union Framework Programme 6, Systems Biology has only recently emerged. A series of workshops on bioinformatics and computational systems biology suggest however that Systems Biology is likely to play a greater role in future EU funding initiatives [1]. There are however already smaller but well defined systems biology projects funded within the EU FP6 programme. One project (COSBKS) that is currently initiated is a joint effort of Rostock University (O. Wolkenhauer), the German Cancer Research Institute (DKFZ) in Heidelberg (U. Klingmüller), the Freiburg Centre for Data Analysis and Modelling (FDM, J. Timmer) in Germany, the

Beatson Institute for Cancer Research in Glasgow (W. Kolch), the Instituto de Investigaciones Marinas (C.S.I.C.) in Vigo, Spain (J. Banga) and the Institute of Mechanics and Biomechanics Bulgarian Academy of Sciences in Sofia, Bulgaria (V. Petrov). The COSBICS project investigates cancer related signal transduction pathways, using a systems biology approach. Based on quantitative immunoblots and supported by microscopy data, mathematical models that are based on nonlinear differential equations are derived in close collaboration with experimentalists. Instead of simply mapping the proteins in a pathway, COSBICS is concerned with “dynamic pathway modelling”, where parameter values are extracted directly from experimental time series. The project considers two signalling systems, independently and with respect to their interactions: The JAK-STAT pathway and the Ras/Raf/MEK/ERK pathway. Both systems are at the heart of a network that governs cell growth, differentiation and survival. The theoreticians in COSBICS investigate the role of feedback loops in control and regulation, spatio-temporal modelling, and parameter estimation. Different modelling paradigms are compared with regard to their value in supporting the design of experiments. Another important aspect of the COSBICS project is the interdisciplinary training programme for young researchers.

References

- [1] The workshop reports were produced within the thematic area ‘Life sciences, genomics and biotechnology for health’ and are available at www.cordis.lu/lifescihealth/genomics

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ANNEX 7

<p>What advantages might systems biology offer to plant science?</p>	<ul style="list-style-type: none"> • Discipline: data collection, analysis and design • Genotype to phenotype: from models to crops/ecosystems • Prediction; gene function, basis of complex traits/natural variation (environment) • Integrative models across scale 	<p><i>Formal representation as a ‘system’ allows</i></p> <ul style="list-style-type: none"> • Better comparison between organisms • Databases with common access language • Integration of disciplines/holistic • Scalability/hierarchies represented through sub-systems that can be stitched together through universal modelling language. • Opportunity to evolve models <i>in silico</i> 	<ul style="list-style-type: none"> • Need to define biological problem – gene identification, development and metabolism, model to crop [species]. • Uncover new information from existing datasets and genetic resources – e.g. maximising information from single gene knockout lines • Quantification for model generation • Prediction aids experimental design 	<ul style="list-style-type: none"> • Additional tool(s) and opportunities, e.g. single cell sampling (in planta) • Ability to move across scales – pathways to landscape • Mathematical abstraction with predictive power – maximising information capture from large datasets. • Interaction with theoreticians; re-evaluate your assumptions, formalise your questions - new way of thinking about science • Exploit developments from single cell SB e.g. development of pathways maps
<p>What areas of plant science might be particularly amenable to such approaches?</p>	<ul style="list-style-type: none"> • Development • Secondary metabolism • Complex traits • Terminal processes e.g. cell death, senescence, flowering • Responses to the environment • Plant pathogen interactions, epigenetics 	<p>[The question “amenable problems in plant science” was paraphrased to “Advantages of plant science”.]</p> <ul style="list-style-type: none"> • Recombinant inbred lines / association mapping: opportunity to identify genes specifying variations in system properties. • Spatial organisation can be exploited: leaf as a system, including young, old, guard cells, growth, senescence, stress, environmental change, sink to source, diverse cell types. • The system is “tweakable”: produce a transgenic plant to alter ‘dose’ of a component, i.e. test hypothesis. 	<ul style="list-style-type: none"> • Applicable to all areas, but focus on a biological problem • Multiscale: molecule, cell, organism, field • Non-linear feedback mechanisms 	<ul style="list-style-type: none"> • All areas amenable: single cells to ecology, landscape • Advantages: Plant development, plants sessile, strength in genetics, breeding, transgenics (in vivo imaging)

<p>What are the current technical and other barriers in applying systems-biology approaches to plant science research?</p>	<ul style="list-style-type: none"> • Perception of plant science: GM debate etc. • Poor communication with other disciplines • Lack of “best practice” for data handling • Lack of examples of good predictive models that have been demonstrated to work • Inability to measure flux • No good homogenous Arabidopsis cell culture 	<ul style="list-style-type: none"> • Spatial heterogeneity (cell types) • Hard to compare datasets grown under different conditions: standards. • No existing comprehensive databases • Modellers/experimentalists must work as one (and this takes time) • Teaching 	<ul style="list-style-type: none"> • Standardisation/organisation of data, including archiving • Cell type – specific data • Long project timescale and critical mass of personnel • Multidisciplinary communication 	<ul style="list-style-type: none"> • Lack of multidisciplinary training (MSc, PhD) • More (and dispersed?) funding for plant systems biology • Bring people together, interactions between comp/math and science (GARNet) • Complicated/frustrated communication links. Plant biologists needs math models of dynamics, kinetics. Comp. science needs biologists to develop common vocabulary (standardisation; SBML?) - “reachness” of ontologies, knowledge (historical) and multiscale data integration, coordination of activities • Difficult to do single cell sampling in plants
<p>What scientific expertise can the UK in particular offer in this context?</p>	<ul style="list-style-type: none"> • Curation/expertise in seeds/data • Resources in genetics/plant breeding • Whole organisms/population biology • Structural biology • Well integrated plant community • Track record in post genomic technology • Good bioinformatics infrastructure? 	<ul style="list-style-type: none"> • Well developed mathematical biology community • Genomics • <i>Arabidopsis</i>/plants community (GARNet) 	<ul style="list-style-type: none"> • Strengths in Plant Science – <i>Arabidopsis</i>, Brassicas and crops, physiology • Hypothesis-driven science • Strong community • Genomics and Bioinformatics 	<ul style="list-style-type: none"> • Broad excellence in plant science, computational biology and informatics • Plant Systems biology education • Resources: Transcriptomic data sets (NASC) / centralised metabolite data analysis (Aberystwyth/Rothamsted) • International strength in plants biochemistry (MCA) • Strong crop community and databases; breeding <i>in silico</i>, running scenarios under different environment – ability to predict phenotypes in changing environments, translate cross

				species, natural diversity
<i>Are there any alternative approaches in plant science to predictive biology?</i>	No!	None or did we misunderstand the question?	No! <ul style="list-style-type: none"> • Looser definition of Systems Biology • Distributed funding and effort • Build on previous Arabidopsis community model 	Plant science is predictive.